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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/718,355	11/24/2000	Guy A. Rouleau	GOUD:023US/10112102	3085

32425 7590 04/22/2009
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ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
04/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/718,355	ROULEAU ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-55 and 60-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-55,60,61 and 65* is/are rejected.

7)☒ Claim(s) *62-64* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks filed 6 November 2008 and the claim amendments filed 19 December 2008 have been entered. Claims 42 - 55 and 60 - 65 are pending and under examination.

Withdrawn Rejections and Objections

2. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 102(b) over Noda is withdrawn in light of the amendments. Independent claim 42 now requires that the SCN1A protein either be identical to SEQ ID NO:3 or 4, or be encoded by a nucleic acid at least 95% identical to disclosed sequences wherein one of a few explicitly recited mutations is present in the encoded protein. The recited mutations are not taught or suggested by Noda.

B. The rejections under 35 USC 103(a) as obvious over Noda in view of Hartshorne (paragraph 6 spanning pp. 5 - 6 of the office action mailed 6 May 2008) and Kienle (paragraph 7 spanning pp. 6 - 7 of the office action mailed 6 May 2008) are withdrawn in light of the amendment to claim 42. As set forth above, claim 42 is no longer anticipated by Noda. The references by Hartshorne and Kienle addressed the specific limitations of claims 48 and 52 respectively but do not address the deficiencies of Noda. Note however the new rejections under 35 USC 103(a) of claims 48 and 52 necessitated by applicant's amendment.

Maintained Rejections

Priority

3. Applicant is reminded that the effective filing date of claims 42 - 53, 60, 62, and 65, each of which recites the D188V mutation or depends from a claim that recites same, is the date the instant application was filed, 24 November 2000. Claims 54 - 55, 61, and 63 – 64 are entitled to benefit of the provisional application, so the effective filing dates of those claims is 26 November 1999, the date 60/167623 was filed.

The reasons why claims encompassing the D188V mutation are denied priority to the provisional application were set forth in the office action mailed 6 May 2008. Applicant did not traverse the examiner's determination that the D188V mutation is first described in the present specification.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda (1987. Journal of Receptor Research 7:467-497) in view of Wood (WO 97/01577, published 16 January 1997), Malo (1994. Cytogenet Cell Genet 67:178-186, cited as reference C2 on IDS filed 28 March 2003), and Current Protocols in Molecular Biology (1989 – 1996, pages 6.0.3 – 6.0.5, 6.1.1 – 6.1.4, 6.3.1 – 6.3.6, and 6.5.1 – 6.5.2).

This rejection is maintained for the reasons previously made of record. The reasons why the claims are obvious were set forth in the office action mailed 6 May 2008 and will be summarized rather than repeated in detail herein. Briefly, Noda teaches screening sodium channels for antagonists which bind to the channels including STX and TTX. Noda teaches recombinant cells comprising rat sodium channels, which are relevant to claims 42, 54, and 61, drawn to methods of screening wild-type sodium channel. However Noda teaches the rat sodium channel, and does not specifically teach methods of using a sodium channel protein with the sequence of SEQ ID NO:3, encompassed by claims 42 and 54. SEQ ID NO:3 is the human adult form of human sodium channel 1A (specification, p. 27, lines 16 – 17).

Wood teaches a number of screening methods with recombinant sodium channels, and teaches that they are useful for identifying new drugs. Wood also teaches that when a sodium channel from one species is known, and nucleic acid encoding the channel is in hand, one can screen a cDNA library made from a second species in order to obtain the nucleic acid encoding the same protein from the second species. Note that Wood indicates while certain examples discuss rat sequences, human sequences can also be used. Wood also teaches alternative methods to identify human sodium channel sequences, by using PCR, and teaches how to confirm that the appropriate clone has been obtained with an *in vitro* assay. However while Wood teaches these methods relating to sodium channels expressed in the periphery, the reference does not explicitly teach sodium channels encoded by the nucleic acid sequence of SEQ ID NO:3, as encompassed by claims 42, 54, and 61.

Malo teaches nucleic acids which are partial sequences of human sodium channel 1 alpha, also known as SCN1A. Note that Figure 3 shows substantial identity between the human SCN1A sequence and that rat Scn1a (also called RBI) sequence at the amino acid and nucleic acid levels. While the human sequence is obviously only a partial sequence, at both the nucleic acid and amino acid levels, the high degree of homology between the identified human sequences and the rat sequence known in the prior art suggests to the artisan of ordinary skill that the full-length human sequence could be obtained. Malo teaches that the partial sequence was obtained by PCR on a human genomic library (p. 179 first column). However Malo does not teach the full-length sequence of SEQ ID NO:3, or nucleic acids encoding the full-length sequence, and does not teach the screening assays recited in claim 42.

Current Protocols Chapter 6 excerpts teaches the artisan of ordinary skill how to screen a DNA library to obtain clones. The specific techniques and protocols necessary for the experiments are detailed, and troubleshooting tips are presented. Chapter 6.1 teaches the artisan of ordinary skill how to plate libraries and transfer them to filters; Chapter 6.3 teaches how to hybridize a DNA probe to the filters, and Chapter 6.5 provides guidance in isolating the appropriate clone. However Current Protocols does not teach either sodium channels or screening assays.

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to screen a human DNA library in order to obtain a full-length clone encoding SCN1A and to use such a nucleic acid in the screening assays described by Noda, with a reasonable expectation of success. The motivation to do so would be to find inhibitors of human sodium channels, instead of rat sodium channels used by Noda. This motivation comes directly from the references themselves; note that Malo teaches that human tissues express SCN1A-encoding nucleic acid, and teaches that such nucleic acids can be obtained by screening libraries. The artisan of ordinary skill would have a reasonable expectation of success in obtaining full-length nucleic acid encoding human SCN1A (i.e., encoding the protein of SEQ ID NO:3), given that Noda provides the full-length rat sequence and Malo provides a partial human sequence. Following the guidance set forth in these references, the artisan of ordinary skill would arrive at the invention of claims 42, 54, and 61, as human SCN1A is in fact the protein of SEQ ID NO:3 and is encoded by SEQ ID NO:1.

At pp. 11 - 12 of the remarks filed 6 November 2008, applicant traverses the examiner's determination that the claimed limitation would have been obvious to one of ordinary skill in the

art. Specifically, applicant argues that since none of the cited references explicitly teaches the sequences of SEQ ID NO:1 or 3, and none of the references provides guidance as to how to make these particular sequences, methods of using those sequences (i.e., the claims subject to this rejection) could not possibly have been obvious. Applicant argues that the Supreme Court's conclusions in *KSR v. Teleflex* that problems with a finite number of possible solutions may be obvious to try should not be extended to the comparatively unpredictable field of biotechnology in general or picking DNA sequences out of a large number of possible sequences in particular.

Applicant's arguments have been fully considered but they are not persuasive. The reference by Malo clearly indicates that partial sequences of the human nucleic acid were known. Obtaining the rest of the human sequence would not have been the result of innovation, but of routine work and experimentation. At the time the invention was made, obtaining full-length cDNAs once a probe or partial sequence was in hand was routine. The methods to obtain such full-length cDNAs were described in Current Protocols, a standard laboratory manual.

The present fact pattern is similar to that in *Ex Parte Kubin* (83 USPQ 2d 1410, Bd Pat App & Int 2007; note a copy of the decision is available at the USPTO's website, the address is http://www.uspto.gov/web/offices/dcom/bpai/prec/fd070819.pdf). In *Kubin*, the Board upheld the Examiner's position that obtaining a full-length nucleic acid by cloning methods would have been obvious. See in particular pp. 7 - 10 of the Board's decision (as published on the USPTO website). Note that the Board determined that given the Supreme Court's recent decision in *KSR v. Teleflex* (127 S. Ct. 1727), the "obvious to try" rationale can be applied; see also MPEP § 2143, subsection E, Example 3. The Board's decision was recently upheld by the Court of Appeals for the Federal Circuit, the decision is available on the internet at http://www.cafc.uscourts.gov/opinions/08-1184.pdf . Note that the CAFC's decision appears to extend the "obvious to try" doctrine set forth in *KSR* to a case where a novel nucleic acid was claimed when the prior art provided sufficient guidance in methods to obtain the nucleic acid. The examiner has concluded that given the teachings of the prior art references, it would have been obvious to one of ordinary skill in the art to follow the guidance in Current Protocols to obtain the human cDNA encoding SEQ ID NO:3. Therefore the rejection under 35 USC 103(a) stands.

5. Claims 42 - 47, 49 - 51, 53 - 55, and 60 - 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda in view of Wood, Malo, and Current Protocols as applied to claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 above, and further in view of Avanzini (1996. Progressive Nature of Epileptogenesis (Epilepsy Res. Suppl. 12), pp. 53 – 61, of record) and Soares (U.S. Patent 5,482,845, issued 9 January 1996).

This rejection is maintained for the reasons previously made of record. Briefly, although none of Noda, Wood, Malo, or Current Protocols explicitly teach nucleic acids encoding the neonatal form of human SCN1A, as encompassed by claim 55, the additional references by Avanzini and Soares render obvious this nucleic acid.

Avanzini teaches that there are several forms of epilepsy which are unique to human infants and which have onset at very early age (<1 yr., see Avanzini p. 53 first column). Avanzini teaches that there has been difficulty in reproducing the features of these early infantile forms of epilepsy in animal models, thereby indicating to the artisan of ordinary skill that there is a need to screen for agents which could treat epilepsy in humans. Avanzini teaches performing experiments with neural tissue from juvenile rats (see Methods section), and teaches that in juvenile tissue inhibitory post-synaptic potentials are not present (p. 53 second column), indicating neurons are likely to be hyper-excitable. Avanzini teaches contacting tissue comprising juvenile rat sodium channels with TTX (p. 54 second column). However Avanzini does not teach performing screening assays to find drugs which reduce sodium channel activity in recombinant neonatal sodium channels.

Soares teaches cDNA libraries from neonatal infant brain, which is on point to claim 42 part (ii) and claim 55, as SEQ ID NO:4 is the neonatal form of the sodium channel; see specification p. 27 lines 17 – 18. The reference provides detailed instructions on how to make such a library, and how to normalize it. However, Soares does not explicitly teach nucleic acids encoding sodium channels and does not teach screening assays as recited in claim 42.

It would have been obvious to one of ordinary skill in the art to screen the human neonatal brain cDNA library from Soares, obtain the neonatal form of the SCN1A channel, and use it in the screening assays described by Noda and Wood, with a reasonable expectation of success. The motivation to do so would be to identify agents to treat epilepsy in juvenile humans, as Avanzini teaches that the animal models do not reproduce this disease well. It would be reasonable to expect success, as Avanzini teaches that those manipulations which

affect sodium currents (i.e., those which pass through sodium channels) are effective in blocking bursts of neural activity (pp. 57 – 58), which are associated with epilepsy.

Applicant argues, on p. 12 of the remarks, that since none of the references teach the actual sequence to be used, the sequence cannot possibly be obvious. The examiner concedes that none of the references spell out the exact sequence. However, since there is motivation to obtain the sequence (see Avanzini) and guidance as to how to prepare cDNA libraries from neonatal sources (Soares) as well as how to screen the library (Current Protocols), obtaining the nucleic acid encoding the neonatal form of the human SCN1A protein would not have been the result of a patentable contribution, but rather of routine experimentation. Thus the rejection is maintained.

Rejections Necessitated by Amendment

Claim Rejections - 35 USC § 103

6. Claims 42 - 51, 53 - 54, and 60 - 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda in view of Wood, Malo, and Current Protocols as applied to claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 above, and further in view of Hartshorne (1984. Journal of Biological Chemistry 259:1667 – 1675, cited in office action mailed 16 April 2007).

The reasons why claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 are obvious over Noda in view of Wood, Malo, and Current Protocols are set forth above. While the references render obvious the screening assays of claim 42, none of the cited references teach cell-free assays as recited in claim 48.

Hartshorne teaches purifying sodium channels to homogeneity from tissue and teaches that the purified channels are able to bind STX. The reference teaches that the isolation process increases the concentration of sodium channels over 1300-fold. However Hartshorne does not explicitly teach screening methods as recited in claim 42.

It would have been obvious to one of ordinary skill in the art to use the cell-free binding assays described by Hartshorne in the screening assays of Noda, with a reasonable expectation of success. The artisan of ordinary skill would be motivated to use the purified channels and cell-free binding assay, because doing so would allow the artisan to use considerably less of the agents to be screened, thereby reducing costs. The *in vitro* cell-free binding assay would be advantageous, because it can easily be scaled up to allow for screening of many agents, whereas the scaling up an *in vivo* assay such as that described by Noda would

be difficult and expensive, given the high cost of electrophysiological recording equipment. This would have been immediately obvious to the artisan upon reading the references, as the Hartshorne reference teaches that STX-binding activity is retained, and the substantial increase in purity would mean that much less of a candidate compound would be needed in a given reaction volume.

7. Claims 42 - 47, 49 - 5, 53 - 54, and 60 - 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Noda in view of Wood, Malo, and Current Protocols as applied to claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 above, and further in view of Kienle (1997. Biosensors and Bioelectronics 12:779-786, cited in office action mailed 16 April 2007).

The reasons why claims 42 - 47, 49 - 51, 53 - 54, and 60 - 61 are obvious over Noda in view of Wood, Malo, and Current Protocols are set forth above. While the references render obvious the screening assays of claim 42, none of the cited references teach using surface plasmon resonance, as recited in claim 52, to detect the interaction between the putative antagonists and the channel.

Kienle teaches use of surface plasmon resonance, as recited in claim 52, to identify agents which bind to rat cardiac sodium channels, which are functionally similar to the sodium channels in claim 42. The reference by Kienle teaches that surface plasmon resonance is a powerful tool that offers many advantages in identifying interactions between a ligand (for example, an antagonist) and a receptor (i.e. a channel). These advantages are listed on p. 779 second column and include that the technique allows for label-free detection, and that it is direct and non-invasive. Further the technique allows for measurement of kinetic rate constants and affinity constants, both of which are useful for the artisan to know when developing drugs. However, Kienle does not teach screening assays using the specific sodium channels recited in claim 42.

It would have been obvious to one of ordinary skill in the art to modify the assays of Noda, which screen for antagonists that bind to sodium channels, to include the surface plasmon resonance technique taught by Kienle, with a reasonable expectation of success. The motivation to modify the assays would be to take advantage of the addition information provided by the surface plasmon resonance technique, including kinetic rate and affinity constants. Given that the remaining references (Wood, Malo, and Current Protocols) render obvious the method of claim 42, dependent claim 52 is obvious given the teachings of Kienle.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 65 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 65 is confusing because it requires that the protein encoded by a nucleic acid have a D→V mutation at residue 188, while simultaneously the protein must be encoded by SEQ ID NO:1 or 2. SEQ ID NO:1 and 2 do not encode proteins with a D→V mutation, so it is unclear whether the claim is directed to methods of using wild-type proteins, i.e. those encoded by SEQ ID NO:1 or 2, or mutant proteins with a D→V mutation.

Conclusion

9. Claims 42 - 55, 60 - 61, and 65 are rejected.

10. Claims 62 - 64 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
April 21, 2009